arousing concern. Programmes already in place require full support to ensure optimal functioning. Other districts may need encouragement to examine their services for this deserving group of patients.[10]

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Ames, the Ames test, and the causes of cancer

Mitogenesis v mutagenesis

Bruce Ames is best known for developing the Ames bacterial mutation test, now widely used as an in vitro assay for detecting potential environmental carcinogens.[1] Ironically Ames is now at the centre of a controversy concerning the causes of cancer, in which he advocates that environmental exposure to manufactured chemicals may be of limited relevance to human cancer, even when such chemicals are mutagenic in an Ames test and carcinogenic in rodent assays.[2-17]

Ames contends that most human genetic damage arises from the oxidation of DNA during normal metabolism. Moreover, he argues that additional mutagenic exposure from the environment results mainly from tobacco smoke, various natural compounds produced by plants to defend themselves, and products that are formed when food is cooked; compared with these sources, the mutagenic burden imposed by environmental exposure to manufactured chemicals is negligible.

Some of the damaging effects of these hazards are counterbalanced by dietary or other antioxidants (which mainly come from fruit and vegetables) and by various mechanisms for DNA repair. Ames argues that these protective mechanisms are less effective when stem cells are put under conditions of chronic proliferative stress and that exposure to agents that accelerate the rate of stem cell division in human tissues can increase the rate at which somatic mutations "escape" repair and become established. As a consequence he suggests that the most important environmental carcinogens may include some whose chief effect is to cause the chronic division of stem cells.

This reasoning is, in itself, neither new nor controversial. It has long been known, for example, that slowly dividing tissues rarely develop tumours.[18] The primacy given to mitogenesis has, however, caused controversy. It leads Ames to take issue with the philosophy underlying current procedures for rodent carcinogenicity testing. He believes that administering artificially high doses of chemicals to rats and mice will often lead to false positive results for carcinogenicity. This is because, for many chemical exposures at or near the toxic doses used, injured cells will exhibit a chronic mitogenic response not otherwise observed and will be especially susceptible to cancer induction.

At the considerably lower doses which approximate to levels of human exposure, little or no mitogenic response occurs and therefore many chemicals will be largely or wholly non-carcinogenic. In other words, Ames is questioning a fundamental assumption that is usually made in these experiments—namely, that an approximately linear dose-response extrapolation from high to low doses is justified.

This leads Ames to disagree with those who advocate, for example, massive efforts to remove trace quantities of synthetic pesticide residues from food or drinking water on the basis of positive animal test results. He has particularly highlighted the potential absurdity of banning certain pesticides such as daminozide (Alar) if the effect of doing so is to increase substantially the total ingestion of mutagenic chemicals from the fungal contaminants and endogenous pesticides in untreated or "organic" crops.[17] He is also concerned that overzealous attention to these issues may divert scarce financial resources away from major health risks and cause public confusion about the relative importance of different hazards.

Ames has provoked a vigorous response, the main thrusts of which have been to defend the use of linear dose-response extrapolation and to question the importance of endogenous oxidative DNA damage in carcinogenesis.[3 5 7 9 11 15 16] His critics also argue that animal and in vitro test results are often the only data available for making informed regulatory decisions. If a chemical causes cancer in rats or mice then there will be concern at human exposures; without evidence to the contrary, an assumption of linear extrapolation in cancer risk is said to be the only prudent option.

Reaching definite conclusions about the regulatory implications of Ames's hypotheses would be premature. Some control of exposure to mutagens and animal carcinogens is necessary (especially in occupational environments). Ames has made us aware that such control may have only a limited impact on the overall burden of cancer.

Ames's view is supported by certain observations from cancer epidemiology. Although tissues that are evolved to divide rapidly may be relatively safe, many important risk factors for human cancer strongly affect cell division.[18] Most notable are the exogenous and endogenous steroid hormones, which have a crucial role in cancers of the breast, ovary, and endometrium and which act by inducing the proliferation of cells.[19] In addition, infectious agents such as the hepatitis B virus, *Opisthorcis viverrini* (liver fluke), and *Schistosoma haematobium* stimulate cell division and are important risk factors for cancer in developing countries. Even tobacco smoke, which is known to contain many mutagens, may act partly as a result of its chronic inflammatory properties.[18] Ames's central message is about distinguishing substantial human risks from inconsequential ones. By reopening this debate Ames is asking the medical and scientific community

to think about which causes of cancer matter in the real world.[20,21]

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Treating bony metastases

Bisphosphonates look promising but their use should await the results of current studies

Solid cancers frequently metastasise to the skeleton, meaning that metastatic bone disease is a common problem in the management of advanced cancer. Necropsy studies show that 85% of women dying of breast cancer have bony metastases; the corresponding proportions for patients with prostatic and lung cancer are 85% and 60%.[1] With meticulous pathological and histological examination the true prevalence of skeletal disease in patients with advanced forms of these common cancers would probably be even higher.

Involvement of bone is not necessarily a late complication of malignancy. Depending on the methods used to detect tumour cells reports have estimated that 20-50% of patients with small cell lung cancer have tumour cells in their bone marrow on presentation.[2] Mansi *et al* also reported that one in four women undergoing surgery for primary breast cancer had metastatic spread to the bone marrow.[3] The morbidity from skeletal involvement is considerable, and bony metastases are the commonest cause of cancer pain.[4] They also cause immobility, pathological fractures, failure of bone marrow, compression of the spinal cord, and hypercalcaemia. Patients with breast cancer whose metastases are limited to bone tend to survive longer than those with metastases at other sites[5] and may therefore have prolonged morbidity. Currently the management of patients with skeletal metastases is directed towards palliating symptoms; only in certain rare cases is cure a realistic aim. Treatment may encompass the specialties of radiotherapy, oncology, surgery, and palliative care, with the contribution from each depending on the type of tumour, stage of disease, and local resources.

External beam radiotherapy is the best treatment for localised metastatic bone pain and is successful in about 85% of cases, although relief may not be experienced for two weeks. A single dose seems to be as effective as fractionated treatment and is clearly more convenient.[6] The role of radiotherapy in asymptomatic lesions or in impending pathological fracture is, however, less clear. Radiation may also be delivered by bone seeking isotopes, and many patients with prostatic cancer have reported pain relief after this treatment.[7]

For pathological fractures of weightbearing bones internal fixation is usually required. Surgical stabilisation of large or painful bone lesions, particularly those with extensive cortical destruction, is also often undertaken if pathological fracture seems likely.[8] Specialised centres often perform more aggressive prosthetic surgery and report worthwhile pain relief and the preservation of skeletal integrity.[9] The true place of these procedures in the routine management of patients with bony metastases, however, has not been established.

Systemic treatment for bone metastases depends on the type of tumour. Endocrine treatment is usually preferred for patients with breast and prostatic cancer. Response rates vary from 20% to 50% in breast cancer[10] and from 60% to 90% in prostatic cancer,[11] the median duration of response being about 12-20 months. Dramatic pain relief is often reported shortly after the start of treatment.[12] Cytotoxic drugs are also used when endocrine treatment fails in patients with bony metastases from breast cancer, but response rates are usually lower and durations of response shorter.[12]

The inadequacy of currently available treatments and the considerable morbidity associated with bony metastases have led to the search for newer and more effective treatments. In this, our increased understanding of normal and pathophysiological bone biology have helped. Turnover of bone is a tightly regulated physiological process, and normally resorption and formation of bone (the actions of osteoclasts and osteoblasts, respectively) are closely linked. Destruction of bone, an integral part of the formation of lytic metastases, is substantially mediated by osteoclasts, and tumours that metastasise to the skeleton often release diffusable substances capable of stimulating osteoclasts to resorb bone.[13] Inhibiting this osteoclastic overactivity therefore represents a possible therapeutic target in the systemic treatment of bony metastases. Several studies have examined the clinical effects of calcitonin, mithramycin, and gallium nitrate (which inhibit osteoclastic resorption of bone),[14-16] but most current interest concentrates on bisphosphonate drugs.

Bisphosphonates are enzyme resistant analogues of pyrophosphate, the naturally occurring inhibitor of mineralisation of bone. Although much is known about the physicochemical properties of these drugs, how they inhibit osteoclastic bone resorption is not fully understood.[17] Bisphosphonates have been used successfully to treat Paget's disease of bone[18] and malignant hypercalcaemia[19-21]: syndromes characterised by abnormal or excessive osteoclastic activity. Currently available drugs include etidronate (which